Original Article

Development and Validation of a Predictive Model for Atrial Functional Mitral Regurgitation

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Abstract

Background: **Identifying atrial etiology in patients with mitral regurgitation remains challenging because the diagnosis is often established by exclusion. The use of a multivariable model may enhance diagnostic accuracy in the context of atrial functional mitral regurgitation.**

Objective: **To develop and validate a multivariable logistic regression model based on clinical and echocardiographic characteristics to predict atrial functional mitral regurgitation.**

Methods: **This cross-sectional study included patients with significant mitral regurgitation diagnosed by transesophageal echocardiography. The dataset was randomly divided into a training set (70%) and a validation set (30%). Statistical analyses were performed using a significance level of 5%.**

Results: **A total of 203 patients were included. The median age was 79 years in the atrial group and 72 years in the non-atrial group (p = 0.0022). Receiver operating characteristic curve analysis demonstrated good discriminative performance, with an area under the curve of 0.896 (95% CI, 0.845-0.947) in the training set. In the validation set, the model achieved an area under the curve of 0.946 (95% CI, 0.89-1.00), which indicates high predictive accuracy. Model calibration assessed by the Hosmer-Lemeshow test (chi-square test = 5.197; df = 8; p = 0.736) demonstrated good agreement between predicted and observed outcomes.**

Conclusion: **A multivariable model was derived and validated as a useful tool for predicting atrial etiology in patients with mitral regurgitation, potentially reducing diagnostic variability in clinical practice.**

Keywords: **Mitral Valve Insufficiency; Echocardiography; Statistical Models; Logistic Models.**

Introduction

Mitral regurgitation (MR) is one of the most prevalent valvular heart diseases in clinical practice and is associated with substantial cardiovascular morbidity and mortality.[1,2] Atrial functional MR (AFMR) initially arises from mitral annular dilation secondary to atrial remodeling; however, recent evidence suggests the involvement of multiple mechanisms, including alterations in atrial compliance and changes in the geometry of valvular apparatus.[1,3] Large echocardiographic registries estimate that AFMR accounts for approximately 40% of cases of moderate to severe functional MR. Early identification of AFMR facilitates the maintenance of sinus rhythm and the timely implementation of interventions, such as catheter ablation, which may attenuate disease progression.[4] In contrast to ventricular functional MR (VFMR), which is primarily associated with left ventricular dilation and systolic dysfunction, AFMR is characterized by isolated atrial remodeling with preserved left ventricular systolic function.[5]

AFMR is marked by left atrial dysfunction resulting from elevated intracavitary pressure, leading to dilation of the left atrium and the mitral annulus, alterations in leaflet concavity (the so-called "saddle-shaped" configuration), and planar leaflet coaptation. Posterior displacement of the mitral annulus toward the ventricular inflow tract further contributes to the regurgitant mechanism.[1,6] These findings reflect atrial remodeling and dynamic changes of the mitral annulus, commonly observed in clinical settings such as atrial fibrillation (AF) or heart failure with preserved ejection fraction (HFpEF). Despite these characteristic features, the diagnosis of AFMR is frequently established

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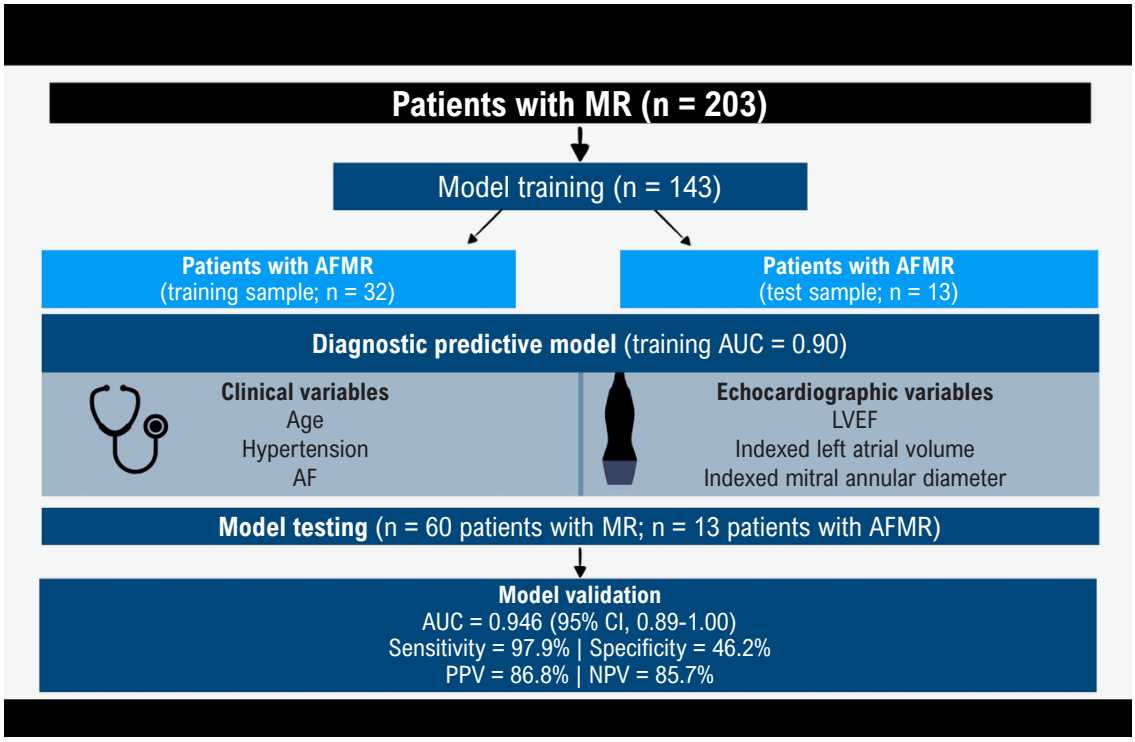
Central Illustration: Development and Validation of a Predictive Model for Atrial Functional Mitral Regurgitation



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Development and Validation of a Predictive Model for Atrial Functional Mitral Regurgitation. MR: mitral regurgitation; AF: atrial fibrillation; AFMR: atrial functional mitral regurgitation; AUC: area under the curve; LVEF: left ventricular ejection fraction; NPV: negative predictive value; PPV: positive predictive value

by exclusion, owing to its overlap with other forms of functional MR.[1] In this context, the development of more structured diagnostic criteria may enhance etiological classification and improve clinical risk stratification in patients with AFMR.[1,7,8]

The severity of AFMR has been associated with adverse clinical outcomes, including increased mortality, heart failure-related hospitalizations, and the need for valvular interventions.[3,8] Patients with AFMR often present with more pronounced symptoms, greater structural remodeling of the left-sided cardiac chambers, and concomitant tricuspid regurgitation, underscoring the increased clinical complexity of this population.[3,9]

The current study aimed to develop a multivariable logistic regression model that integrates clinical and echocardiographic variables in order to distinguish AFMR from other causes of MR. Internal validation of the model was performed using an independent dataset from the initial derivation cohort, thereby enhancing methodological rigor and offering the potential to reduce diagnostic variability in clinical practice.

Methods

Study design and population

This was a prospective, single-center, observational study conducted between October 2022 and January 2025. The study population consisted of 203 consecutive patients with moderate or severe MR who underwent transesophageal echocardiography (TEE) at a tertiary care hospital in Brazil. Patients were included consecutively and by convenience, reflecting routine clinical practice, and were referred for TEE based on clinical indications for reassessment of MR severity or clarification of its etiology.

Patient selection

Eligible participants were adults (≥ 18 years) with a clinical indication for TEE as determined by the attending cardiologists, either in outpatient or inpatient settings, for diagnostic evaluation of MR. Patients with a mitral valve prosthesis or those whose MR severity was reclassified as mild on TEE were excluded from the study.

Echocardiographic assessment

All patients underwent comprehensive two-dimensional transthoracic echocardiography followed by TEE using a Vivid E95 ultrasound system equipped with a phased-array transducer (M5S) (General Electric, Horten, Norway).

MR severity was quantified in accordance with the recommendations of the American Society of Echocardiography, using vena contracta width, regurgitant volume, and effective regurgitant orifice area as objective diagnostic criteria. Qualitative assessment included the proportion of left atrial area occupied by the regurgitant jet and the presence of Coandă effect.[10]

Etiological classification of MR was independently performed by two experienced echocardiographers based on updated diagnostic criteria for AFMR. AFMR was defined by the presence of moderate or severe left atrial enlargement (> 42 mL/m^2), mitral annular dilation (> 35 mm in the parasternal long-axis view or ≥ 36 mm in the apical four-chamber view during systole on transthoracic echocardiography), and the exclusion of diagnostic criteria for alternative MR etiologies.[1]

Other causes of MR were defined according to established guidelines specific to each etiology, including mitral valve prolapse, chordal rupture, calcific degeneration, mitral cleft, and VFMR. Patients were classified into two main groups: atrial and non-atrial etiology.

Statistical analysis

Statistical analyses were performed using R software (version 4.4.2) within the RStudio environment, using appropriate packages for predictive modeling and model performance assessment. Categorical variables are presented as absolute and relative frequencies (%), while continuous variables are reported as median and interquartile range (IQR), as none demonstrated normal distribution. Normality was assessed using the Shapiro-Wilk test.

Comparisons between the atrial and non-atrial groups were conducted according to variable type. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate based on expected cell frequencies. Continuous variables were compared using the Mann-Whitney *U* test. A two-sided significance level of 5% ($\alpha = 0.05$) was adopted for all analyses.

Predictive model development

A multivariable logistic regression model was constructed using the presence of AFMR as the dependent variable. Independent variables were selected based on clinical relevance, absence of significant collinearity, and statistical performance in univariable analyses.

Collinearity assessment

To ensure model stability, collinearity among continuous variables was assessed using the variance inflation factor (VIF). VIF values < 5 were considered indicative of low collinearity and acceptable for inclusion. Values between 5 and 10 were classified as moderate collinearity and required clinical judgment for retention or exclusion, whereas values > 10 indicated severe collinearity and led to variable removal. This process was conducted iteratively to retain only variables with the greatest clinical and statistical relevance.

Model derivation and validation

To robustly assess predictive performance, the dataset was randomly divided into two independent subsets: 70% of patients were allocated to the training set (n = 143), and the remaining 30% to the test (validation) set (n = 60). The split preserved the proportion of AFMR cases and ensured balanced representation across both datasets.

Model discrimination was evaluated separately in the training and validation samples using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC) and corresponding 95% CIs.

In addition to AUC, diagnostic performance metrics including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed across different cutoff points to optimize predictive accuracy.

Model calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test, assessing agreement between predicted and observed probabilities. Calibration performance was further examined through graphical calibration curves, allowing visualization of the alignment between model predictions and observed outcomes.

Results

A total of 203 patients were included in the study, of whom 45 (22.2%) were classified as having AFMR. The cohort was divided into a training set comprising 143 patients (70%) and a test set comprising 60 patients (30%), preserving the proportion of AFMR cases. In the training cohort, 32 patients (22.4%) had AFMR; in the test cohort, 13 patients (21.7%) had AFMR (Central Illustration).

Baseline demographic characteristics in the training cohort demonstrated a median age of 78 years (IQR, 72-84) in the atrial group and 70 years (IQR, 60-78) in the non-atrial group. Male sex was observed in 43.75% of patients in the atrial group and 63.06% in the non-atrial group, although this difference did not reach statistical significance (p = 0.0799) (Table 1).

To ensure model stability and interpretability, a systematic collinearity analysis was performed using VIF to identify and exclude redundant variables. Variables with VIF > 5 were removed to minimize linear dependencies and improve coefficient stability in the logistic regression model. Among anthropometric variables, height and body surface area (BSA) exhibited strong correlation; therefore, BSA was excluded due to its lower incremental informational value. Similarly, the linear mitral annular diameter was excluded in favor of the mitral annular diameter indexed to BSA, which demonstrated lower collinearity and greater clinical applicability (Tables 1 and 2).

After successive iterations of collinearity assessment, six variables were retained for inclusion in the predictive model: three clinical variables (age, hypertension, and

AF) and three echocardiographic variables (left ventricular ejection fraction [LVEF], indexed left atrial volume, and mitral annular diameter indexed to BSA). All retained variables demonstrated VIF values < 2, indicating negligible collinearity. The most statistically significant predictor was indexed mitral annular diameter ($p = 4.81 \times 10^{-7}$), followed by age ($p = 0.0022$) and LVEF ($p = 0.0067$), underscoring their relevance for etiological differentiation (Table 3).

The selection of these predictors was guided by both clinical relevance and statistical significance, ensuring robustness and accuracy of the predictive model (Table 3). This parsimonious set of variables supports improved discrimination of AFMR and may contribute to reduced diagnostic variability and enhanced clinical decision-making.

In the training cohort, the ROC curve analysis demonstrated an AUC of 0.896 (95% CI, 0.845-0.947), which indicates good discriminative performance (Figure 1). Model calibration assessed by the Hosmer-Lemeshow test yielded $\chi^2 = 5.197$, with 8 degrees of freedom ($p = 0.736$), which indicates good agreement between predicted and observed outcomes (Figure 2).

To compare predictive performance across different variable combinations, ROC curves were constructed for three distinct models: a clinical model (clinical variables only), a structural model (echocardiographic variables only), and a complete model (combined clinical and echocardiographic variables). Corresponding AUC values were 0.7974 (95% CI, 0.7264-0.8685), 0.7922 (95% CI, 0.7214-0.8630), and 0.8961 (95% CI, 0.8454-0.9468), respectively (Figure 3).

In the test cohort, the ROC curve analysis demonstrated an AUC of 0.946 (95% CI, 0.8899-1.0000) (Figure 4). At the selected cutoff point, the model achieved a sensitivity of 97.9%, specificity of 46.2%, PPV of 86.8%, and NPV of 85.7%.

Discussion

Mitral annular diameter is widely used in the evaluation of AFMR; however, its diagnostic specificity is limited in the setting of advanced atrial remodeling.[11-13] Previous studies have demonstrated modest discriminative performance of this isolated parameter, prompting the development of multiparametric approaches.[14] In the current study, we developed a multivariable logistic regression model integrating clinical and echocardiographic variables, which demonstrated high discriminative performance consistently confirmed by statistical testing. The structured combination of readily available variables overcomes the limitations of isolated echocardiographic parameters and improves etiological classification of AFMR.

Multiparametric models combining clinical and echocardiographic data have shown value in different contexts of MR. A notable example is the MIDA score, derived from the Mitral Regurgitation International Database, which integrates clinical and imaging variables

Table 1 – Clinical and demographic characteristics of the atrial and non-atrial groups in the training sample

Variable	Atrial (n = 32)	Non-atrial (n = 111)	p-value
Male sex, n (%)	14 (43.8)	70 (63.1)	0.08
Previous CAD, n (%)	8 (25.0)	41 (36.9)	0.30
PCI, n (%)	6 (18.8)	20 (18.0)	> 0.99
Previous MR, n (%)	1 (3.1)	11 (9.9)	0.30
Previous stroke, n (%)	5 (15.6)	17 (15.3)	> 0.99
Diabetes mellitus, n (%)	10 (31.3)	44 (39.6)	0.51
Hypertension, n (%)	27 (84.4)	67 (60.4)	0.02
Dyslipidemia, n (%)	26 (81.3)	63 (56.8)	0.02
Use of beta-blockers, n (%)	17 (53.1)	61 (54.9)	> 0.99
Use of antiarrhythmic drugs, n (%)	12 (37.5)	29 (26.1)	0.30
CKD, n (%)	8 (25.0)	19 (17.1)	0.45
AF, n (%)	23 (71.9)	49 (44.1)	0.01
Use of anticoagulant, n (%)	22 (68.8)	47 (42.3)	0.15
Pacemaker, n (%)	4 (12.5)	17 (15.3)	0.73
Tricuspid regurgitation, n (%)	13 (40.6)	34 (30.6)	0.40
CKD treated by dialysis, n (%)	1 (3.1)	11 (9.9)	0.30

Values with p < 0.05 indicate statistically significant differences. AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease; MR: mitral regurgitation; PCI: percutaneous coronary intervention.

Table 2 – Continuous characteristics of the atrial and non-atrial groups in the training sample

Variable	Atrial median (P_{25}-P_{75})	Non-atrial median (P_{25}-P_{75})	p-value
Age, years	78.0 (72.0-84.0)	70.0 (60.0-78.0)	< 0.001
HR, bpm	92.0 (74.0-118.0)	79.0 (69.0-90.0)	0.015
Weight, kg	70.0 (60.0-80.0)	72.5 (63.0-82.8)	0.410
BSA, m^2	1.8 (1.64-1.85)	1.8 (1.65-1.99)	0.110
LA diameter, mm	46.0 (44.0-49.0)	45.0 (41.0-49.0)	0.049
Indexed LA volume, mL/m^2	62.0 (51.0-78.0)	53.5 (45.0-68.0)	0.004
LVEF, %	61.0 (56.0-64.0)	48.0 (30.0-64.0)	0.002
E/E′ ratio	16.0 (13.9-18.0)	17.0 (10.0-21.8)	0.950
TAPSE, mm	19.0 (18.0-20.0)	19.0 (18.0-21.0)	0.650
Right ventricular S′, cm/s	11.0 (10.0-11.0)	11.0 (9.5-12.0)	0.830
PASP, mmHg	44.0 (40.0-50.0)	40.0 (33.5-51.0)	0.110
Intercommissural mitral annular diameter, mm	36.0 (34.0-40.0)	34.0 (31.0-36.0)	< 0.001
Indexed mitral annular diameter, mm/m^2	21.2 (20.2-22.4)	18.3 (17.0-20.1)	< 0.001

Values with p < 0.05 indicate statistically significant differences. BSA: body surface area; HR: heart rate; LA: left atrium; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure.

Table 3 – Variables included in the diagnostic predictive model for atrial functional mitral regurgitation

Variable	Atrial	Non-atrial	p-value
Age, years	78.0 (72.0-84.0)	70.0 (60.0-78.0)	< 0.001
Hypertension, n (%)	27 (84.4)	67 (60.4)	0.020
AF, n (%)	23 (71.9)	49 (44.1)	0.010
Indexed mitral annular diameter, mm/m^2	21.2 (20.2-22.4)	18.3 (17.0-20.1)	< 0.001
LVEF, %	61.0 (56.0-64.0)	48.0 (30.0-64.0)	0.002
Indexed LA volume, mL/m^2	62.0 (51.0-78.0)	53.5 (45.0-68.0)	0.004

Values with p < 0.05 indicate statistically significant associations, according to the applied test. AF: atrial fibrillation; LA: left atrium; LVEF: left ventricular ejection fraction.

for prognostic stratification in degenerative MR and has demonstrated consistent performance across multiple internal and external cohorts.[15-17] Although the MIDA score was designed for prognostic assessment in primary mitral disease, the present model focuses on improving diagnostic performance for differentiating AFMR. By incorporating routinely available variables (e.g., age, cardiac rhythm, LVEF, and indexed mitral annular diameter), the proposed model addresses a clinically relevant gap for which no dedicated diagnostic tool currently exists, as highlighted in recent research on AFMR.[1,18] Thus, the multiparametric principle appears applicable to both prognostic and diagnostic purposes when appropriately tailored to the clinical context.

Recent population-based studies further emphasize the importance of early recognition of AFMR. In the National Echocardiography Database Australia (NEDA) cohort, which included more than 5,500 patients with moderate to severe AFMR, atrial etiology accounted for approximately 40% of cases and was associated with slightly lower but still substantial mortality compared with VFMR, with a 5-year mortality rate approaching 50%.[4] Complementarily, a longitudinal analysis of 635 individuals with mild to moderate AFMR demonstrated that, even in the absence of overt hemodynamic progression, this entity confers an annual mortality risk of 5.9% and is associated with diastolic dysfunction and pulmonary hypertension.[3]

In this context, real-time differentiation of AFMR from other forms of MR remains challenging. The proposed score incorporates variables validated in large registries such as NEDA and can be calculated during echocardiographic assessment, thereby standardizing etiological classification and facilitating early referral to electrophysiology or heart team evaluation, particularly in centers lacking advanced three-dimensional imaging or with variable expertise.[4] As

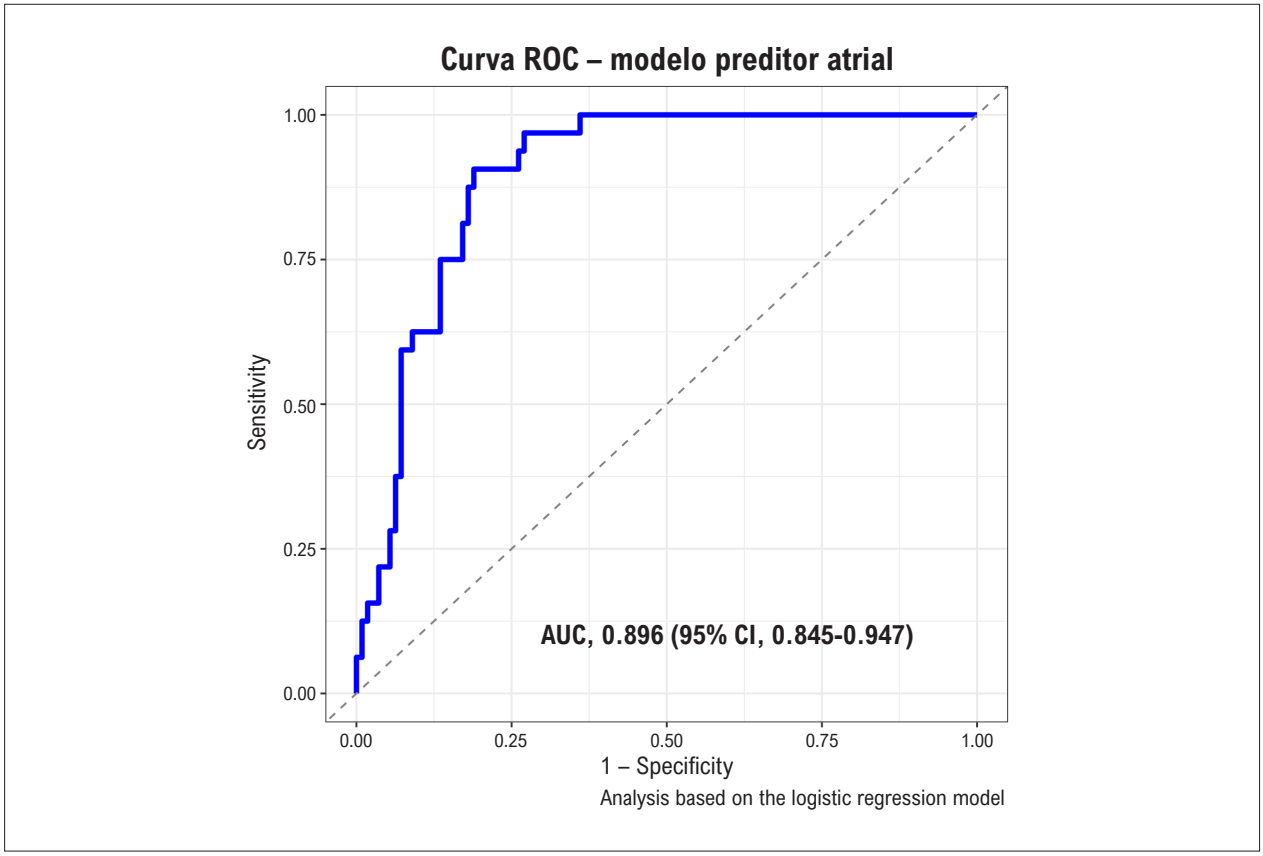

Figure 1 – *Discriminative performance of the atrial etiology predictive model. AUC: area under the curve; ROC: receiver operating characteristic*

a screening tool, the model may assist in identifying AFMR and guiding clinical decisions, including consideration of rhythm control strategies such as catheter ablation or optimization of therapy for HFpEF, with potential implications for follow-up and clinical outcomes.

Internal consistency was assessed using a hold-out validation approach, reserving 30% of the sample for independent testing. This strategy allows evaluation of predictive performance in data not used for model derivation, thereby reducing the risk of overfitting and supporting internal generalizability. Nevertheless, reliance on a single cohort limits assessment of coefficient stability and may underestimate variability across different populations. Additional validation in external cohorts will be required to confirm reliability and expand the clinical applicability of the model.

Study limitations

This study did not incorporate serum biomarkers (e.g., N-terminal pro-B-type natriuretic peptide), atrial strain measurements, electrocardiographic parameters, or three-dimensional quantification of mitral annulus. These additional domains may provide incremental information regarding atrial remodeling and hemodynamic burden, potentially enhancing the discriminative performance of the algorithm. Future studies should evaluate the impact of these markers on diagnostic accuracy and model reproducibility across different clinical settings.[12] Furthermore, international guidelines recommend integrating additional variables in the assessment of valvular regurgitation, which underscores their relevance to clinical practice.[15]

While several multicenter studies have compared AFMR exclusively with VFMR, the present analysis used all non-atrial etiologies, including primary MR, as the reference group.[19,20] This approach was based on two practical considerations: the limited number of isolated VFMR cases, which would have compromised statistical power in both training and test phases, and the intention to evaluate model performance in a real-world scenario characterized by heterogeneous clinical, anatomical, and functional presentations of MR. We acknowledge that such heterogeneity may attenuate the model's ability to distinguish subtle differences between functional subtypes, thereby limiting specific pathophysiological inferences.

From a methodological standpoint, given the number of observed events (45 cases of AFMR) and the number of predictors included in the final model (six variables), the events-per-variable ratio lies at the lower boundary of conventional recommendations for logistic regression, potentially increasing the risk of overfitting. This risk was

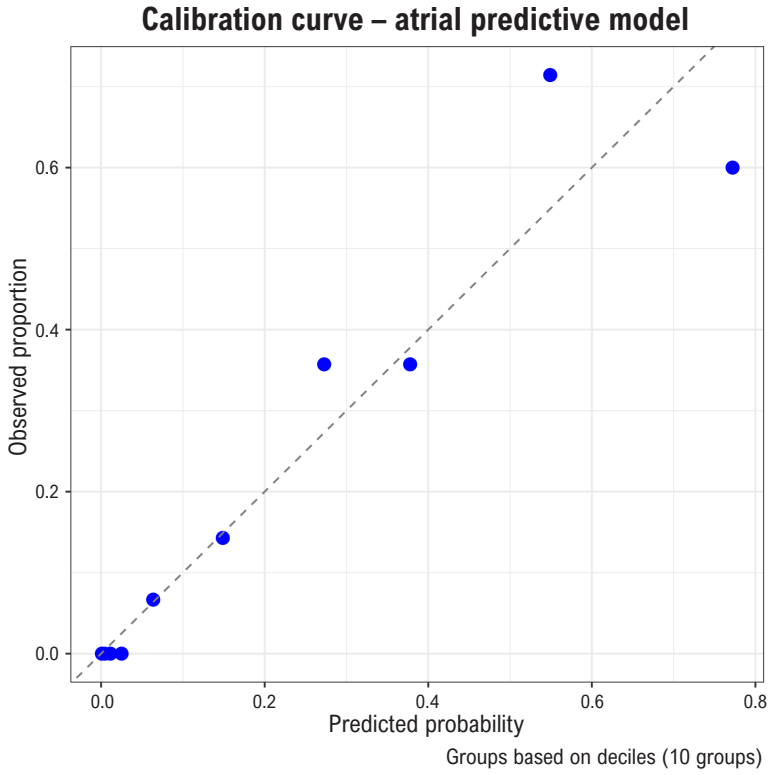

Figura 2 – *Calibration curve of the atrial predictive model.*

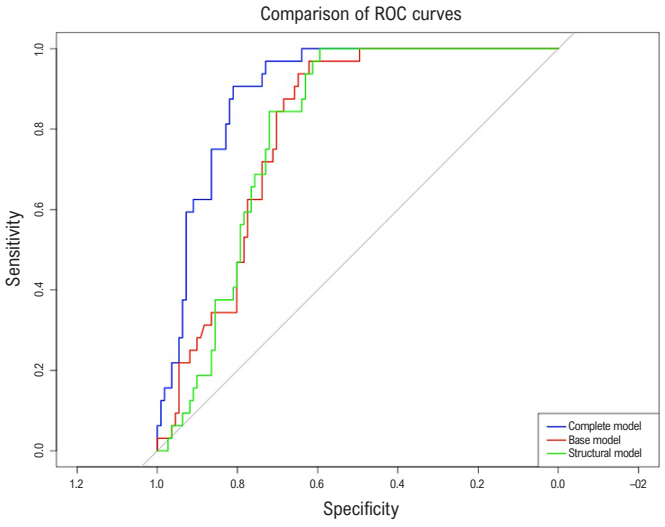

Table – AUC and 95% CI for the three models

Model	AUC (95% CI)
Base (clinical variables)	0,7974 (0,7264–0,8685)
Structural (echocardiographic variables)	0,7922 (0,7214–0,8630)
Complete (clinical + echocardiographic)	0,8961 (0,8454–0,9468)

Figure 3 – *Comparison of ROC curves for clinical, echocardiographic, and combined models. AUC: area under the curve; ROC: receiver operating characteristic*

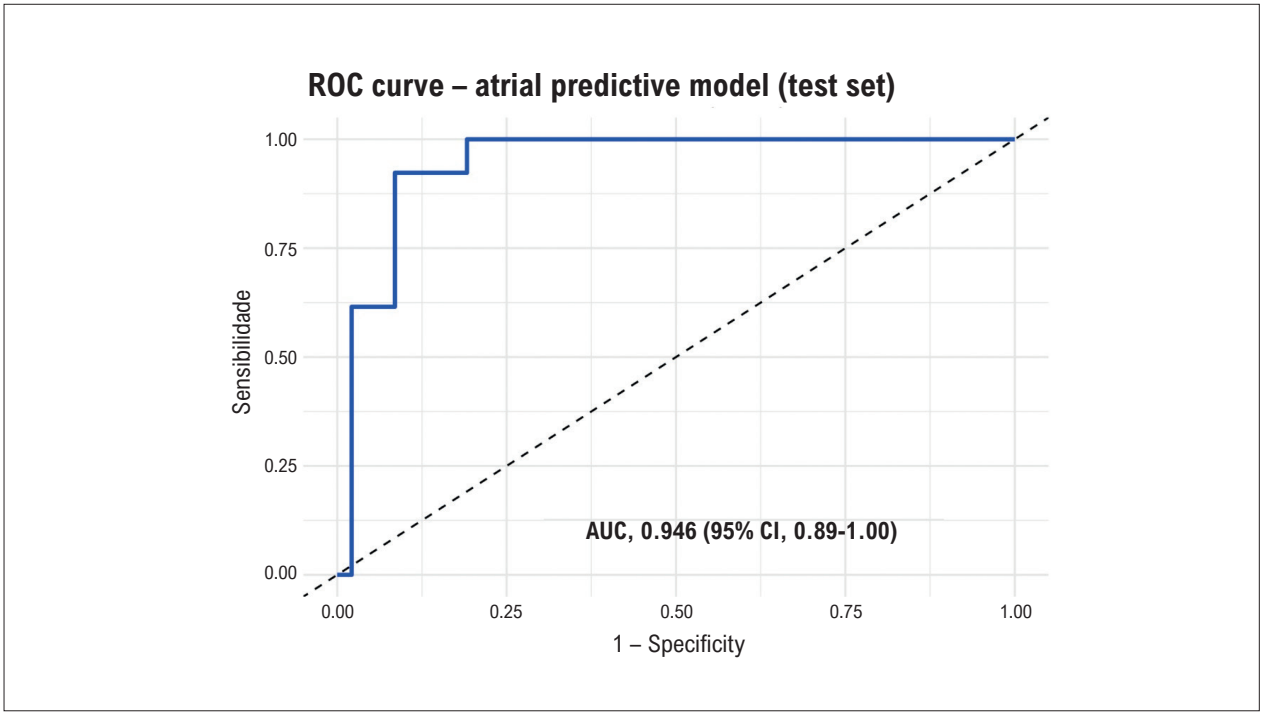

Figure 4 – *ROC curve of the atrial predictive model in the test set. AUC: area under the curve; ROC: receiver operating characteristic*

mitigated through parsimonious selection of predictors with strong clinical and echocardiographic plausibility, as well as systematic collinearity assessment. Additionally, the high AUC observed in the test sample (0.946) should be interpreted with caution since it was derived from a limited number of events in that subset (n = 13), which increases uncertainty and the possibility of performance overestimation. Accordingly, these findings should be regarded as exploratory and require confirmation in independent external cohorts.

Conclusion

The derivation and validation of a multivariable model for predicting AFMR may be clinically useful. Because of the limitations of isolated mitral annular measurements for diagnostic purposes, the integration of echocardiographic and clinical parameters within a unified model demonstrated potential to reduce diagnostic variability, which enables earlier detection and timely interventions that may improve the prognosis and management of patients with AFMR.

Author Contributions

Conception and design of the research and statistical analysis: Souza AC; acquisition of data: Souza AC, Pinheiro P; analysis and interpretation of the data: Souza AC, Filgueiras PHC; writing of the manuscript: Souza AC, Junqueira BMI, Drubi AS, Pinheiro P, Guedes RASP, Gomes LC; critical revision of the manuscript for intellectual content: Junqueira BMI, Sales MAM, Guedes RASP, Macêdo CT; illustration: Filgueiras PHC, Carvalho YX.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital São Rafael under the protocol number 5722007. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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